REMARKS

Claims 39-43 are pending in this application. The present rejections to the claims are respectfully traversed. Claims 39 and 43 have been amended to clarify the claimed invention.

Withdrawn Objections and/or Rejections

Applicants note with appreciation that the objection to claim 43 is withdrawn.

Applicants note with appreciation that the rejection of claims 39-43 under 35 U.S.C. § 102(a) as being anticipated by Wood et al., (WO99/14328) is withdrawn.

Applicants note with appreciation that the rejection under 35 U.S.C. § 103(a) as being unpatentable over Valenzuela et al., in view of Ramakrishnan et al. is withdrawn.

Information Disclosure Statement

Applicants thank the Examiner for considering the Information Disclosure Statement submitted 16 October 2003.

Correction of Inventorship

Applicants note that the Examiner has indicated that the inventorship in this application has been changed. Applicants note that they have yet to receive a corrected filing receipt. Applicants have amended the inventorship to place Goddard as the first inventor as indicated in PAIR.

Rejections under 35 U.S.C. § 101 and 112, first paragraph

Claims 39-43 stand rejected under 35 U.S.C. § 101 because the claimed invention is allegedly not supported by a credible, specific and substantial asserted utility or a well established utility.

Claims 39-43 stand rejected also under 35 U.S.C. § 112, first paragraph. Specifically since the claimed invention is allegedly not supported by either a credible, specific and substantial asserted utility or a well established utility, one skilled in the art would allegedly not know how to use the claimed invention.

Previously Applicant had provided section 1.132 declarations of Audrey Goddard and Avi Ashkenazi discussing the gene amplification assay. The Patent Office indicates that the gene amplification assay provides a patentable utility for the PRO 269 nucleic acid.

However, the Patent Office indicates that the gene amplification assay does not establish a utility for PRO269 antibodies, to which this application is directed. For the reasons outlined below, Applicants respectfully disagree. With respect to claims 39-43, Applicants submit that not only has the Patent Office not established a *prima facie* case for lack of utility and enablement, but that the antibodies of claims 39-43 possess a credible, specific and substantial asserted utility and are fully enabled.

Evidentiary Standard

An Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re* Langer, 503 F.2d 1380,1391, 183 USPQ 288, 297 (CCPA 1974); *see, also In re* Jolles, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re* Irons, 340 F.2d 974, 144 USPQ 351 (1965); *In re* Sichert, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977).

Compliance with 35 U.S.C. § 101 is a question of fact. Raytheon v. Roper, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration. *In re* Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992) Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the PTO must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Only after the PTO has made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the applicant. The issue will then be decided on the totality of evidence.

A *prima facie* case of lack of utility has not been established

The Patent Office bases its conclusion that gene amplification does not reliably correlate with increased mRNA transcript or polypeptide levels, and hence its conclusion that PRO269 polypeptides and antibodies lack utility, on Pennica *et al.*, Konopka *et al.*, and Haynes *et al.*

The Patent Office cites Pennica *et al.* to support its argument that gene amplification does not reasonably correlate with increased mRNA or polypeptide levels. According to the Patent Office, Pennica *et al.* teaches that "[a]n analysis of *WISP*-1 gene amplification and expression in human colon tumors *showed a correlation between DNA amplification and over-expression,* . . . . In contrast, *WISP*-2 DNA was amplified in colon tumors, but its mRNA expression was significantly reduced in the majority of tumors compared with expression in normal colonic mucosa from the same patient." (Emphasis added). Applicants submit that the Patent Office has omitted to disclose that in the same paragraph, Pennica *et al.* also explains that the reason for the absence of correlation between amplification and over-expression may be because the gene while initially believed to be amplified, was not in fact amplified — "it is possible that the *apparent* amplification observed for *WISP-2* may be caused by another gene in this amplicon." Emphasis added. Accordingly, Applicants respectfully submit that Pennica *et al.* teaches nothing conclusive regarding the absence of correlation between amplification of a gene and over-expression of the encoded polypeptide. Further, Applicants do not claim that the utility of the instant invention is the over-expression of *WISP-2* mRNA.

The Patent Office also cites the abstract of Konopka *et al.* to establish that "[p]rotein expression is not related to amplification of the *abl* gene . " Applicants respectfully submit that Applicants do not claim that the utility of the instant invention is the over-expression of the *abl* gene.

Lastly, the Patent Office cites Haynes *et al.*, to show that there was a "general trend but no strong correlation between protein [expression] and transcript levels" for 80 *yeast* proteins. Haynes *et al.*, adds that "[f]or **some** genes, equivalent mRNA levels translated into protein abundances which varied by more than 50-fold." (Emphasis added).

Haynes *et al.* is directed to a study of normally expressed genes in the yeast *Saccharomyces cerevisiae.* Haynes *et al.* identified 80 protein spots which correlated to highly abundant proteins in the cell. There are approximately 6000 gene products in yeast. Haynes *et al.* indicated that they were only able to visualize and identify the more abundant proteins. "Since many important regulatory proteins are present only at low abundance levels these would not be amenable to analysis using such techniques". The statement made by Haynes *et al.* cannot be applied to the current application. Haynes *et al.* was not studying expression in human cells and his system was only able to detect the most

abundant proteins which are not the important regulatory proteins. Finally, Haynes was not looking at the overexpression of proteins in tumor cells.

Based on the above, the Patent Office concludes that increased copy number does not *necessarily* result in increased protein expression. The standard, however, is not absolute certainty. The fact that in the case of a specific class of closely related molecules there seemed to be no correlation with gene amplification and the level of mRNA/protein expression, does not establish that it is more likely than not, in general, that such correlation does not exist.

The PTO has not shown whether the lack of correlation between gene amplification and polypeptide over-expression observed for WISP-2 polypeptides, or the abl gene, or some genes in a family of 80 yeast genes is typical, or is merely a discrepancy, an exception to the rule of correlation. Indeed, the working hypothesis among those skilled in the art is that, if a gene is amplified in cancer, the encoded protein is likely to be expressed at an elevated level. In fact, as noted even in Pennica *et al.*, *a correlation between DNA amplification and over-expression of polypeptide* ***was observed*** *in the case of WISP-1*. Similarly, Haynes *et al.*, state that **some** genes **did** show a correlation between increased mRNA levels and translated protein.

Even if a *prima facie* case of lack of utility has been established, it should be withdrawn on consideration of the totality of evidence

Even if it is more likely than not that there is no correlation between gene amplification and increased mRNA/protein expression, which Applicants specifically deny, a polypeptide encoded by a gene that is amplified in cancer would **still** have a credible, specific and substantial utility. In support, Applicants previously submitted a Declaration by Avi Ashkenazi, Ph.D., an expert in the field of cancer biology and an inventor of the instant application. Dr. Avi Ashkenazi's Declaration explains that:

> even when amplification of a cancer marker gene does not result in significant over-expression of the corresponding gene product, this very absence of gene product over-expression still provides significant information for cancer diagnosis and treatment. Thus, if over-expression of the gene product does not parallel gene amplification in certain tumor types but does so in others, then parallel monitoring of gene amplification and gene product over-expression enables more accurate tumor classification and hence better determination of suitable therapy. In addition, absence of over-expression is crucial information for the practicing clinician. If a gene is amplified but the corresponding gene product is not over-

expressed, the clinician accordingly will decide not to treat a patient with agents that target that gene product.

Applicants thus submit that simultaneous testing of gene amplification and gene product over-expression enables more accurate tumor classification, even if the gene-product, the protein, is not over-expressed. This leads to better determination of a suitable therapy. Further, as explained in Dr. Ashkenazi's Declaration, absence of over-expression of the protein itself is crucial information for the practicing clinician. If a gene is amplified in a tumor, but the corresponding gene product is not over-expressed, the clinician will decide not to treat a patient with agents that target that gene product. This not only saves money, but also the patient need not be exposed to the side effects associated with such agents.

This is further supported by the teachings of the attached article by Hanna and Mornin[1]. The article teaches that the HER-2/neu gene has been shown to be amplified and/or over-expressed in 10%-30% of invasive breast cancers and in 40%-60% of intraductal breast carcinoma. Further, the article teaches that diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene (by FISH) as well as the over-expression of the HER-2/neu gene product (by IHC). Even when the protein is not over-expressed, the assay relying on both tests leads to a more accurate classification of the cancer and a more effective treatment of it.

Thus, Applicants have demonstrated a credible, specific and substantial asserted utility for the PRO269 polypeptide and for antibodies that bind to PRO269, for example, in detecting over-expression or absence of expression of PRO269. Further, based on this utility and the disclosure in the specification, one skilled in the art at the time the application was filed would know how to use the claimed antibodies.

Priority

1. Applicants have asserted priority to PCT International Application No. PCT/US00/03565, filed February 11, 2000

[1] Copy enclosed.

Applicants have previously asserted priority to PCT International Patent Application No. PCT/US00/03565 filed February 11, 2000. This application discloses the PRO269 gene and includes the DNA amplification assay data found in the current application.

The Patent Office has denied the priority claim on the basis that the priority application allegedly lacks utility and enablement for the reasons set forth in the rejection of the instant application. The Patent Office has determined the effective filing date for the instant claims to be 12 July 2001.

Applicants submit that, for the reasons set forth above, the results of the gene amplification assay (Example 92) in PCT/US00/03565 provide specific, substantial and credible utility for the polypeptide PRO269 and the claimed antibodies in this invention. For the reasons set forth above, the PRO269 polypeptide and antibodies are also fully enabled.

2. Applicants have also asserted priority to PCT Patent Application No. PCT/US98/19330, Wood et al., filed 16 September 1998.

Applicants have also asserted priority to PCT Patent Application No. PCT/US98/19330, Wood et al., filed 16 September 1998 in the original declaration filed. Applicants submit that PCT Patent Application No. PCT/US98/19330 simply needs to provide a disclosure commensurate in scope with the disclosure in the cited art to support the priority claim.

In *In re* Stempel (1957) 113 USPQ 77, the patent applicant (Stempel) had claims directed to both (i) a particular genus of chemical compounds (the "generic" claim) and (ii) a single species of chemical compound that was encompassed within that genus (the "species" claim). In support of a rejection under 35 U.S.C. § 102, the examiner cited against the Stempel application a prior art reference that disclosed the exact chemical compound recited in Stempel's "species" claim. In response to the rejection, Stempel filed a declaration under 37 C.F.R. §. 1.131 demonstrating that he had made that specific chemical compound prior to the effective date of the cited prior art reference. The CCPA found Stempel's 131 declaration effective for swearing behind the cited reference for purposes of both the "species" claim and the "genus" claim. Specifically, the CCPA stated in support of its decision:

"We are convinced that under the law all the applicant can be required to show [in a declaration under 37 C.F.R. §. § 1.131] is priority with respect to **so much of the claimed invention as the**

reference happens to show. When he has done this he has disposed of the reference." (Id. at 81; emphasis supplied).

Secondly, the Examiner is respectfully directed to *In re* Moore, 170 USPQ 260 (CCPA 1971), where the Stempel rule was extended to cases where a reference disclosed the claimed compound but failed to disclose a sufficient utility for it. More specifically, the patent applicant (Moore) claimed a specific chemical compound called PFDC. In support of a rejection of the claim under 35 U.S.C. § 102, the examiner cited a reference which disclosed the claimed PFDC compound, but did not disclose a utility for that compound. Applicant Moore filed a declaration under 37 C.F.R. § 1.131 demonstrating that he had made the PFDC compound before the effective date of the cited prior art reference, even though he had not yet established a utility for that compound. On appeal, the CCPA indicated that the 131 declaration filed by Moore was sufficient to remove the cited reference. The CCPA relied on the established "Stempel Doctrine" to support its decision, stating:

An applicant need **not** be required to show [in a declaration under 37 C.F.R. § 1.131] any more acts with regard to the subject matter claimed that can be carried out by one of ordinary skill in the pertinent art following the description contained in the reference....the determination of a practical utility when one is not obvious need **not** have been accomplished prior to the date of a reference unless the reference also teaches how to use the compound it describes. (Id. at 267, emphasis supplied).

Thus, *In re* Moore confirms the Stempel rule holding that in order to effectively remove a cited reference with a declaration under 37 C.F.R. § 1.131, an applicant need only show that portion of his or her claimed invention that appears in the cited reference.

Applicants have claimed priority to PCT Patent Application No. PCT/US98/19330, Wood et al., filed 16 September 1998. Applicants maintain that they should be entitled to priority to this application to remove prior art references with similar disclosures consistent with the teachings of *In re* Stempel and *In re* Moore.

Rejections under 35 U.S.C. §102

1. Claims 39-43 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Wood et al., WO99/14328 (PCT/US98/19330).

A. Applicants are claiming priority to to PCT Application No. PCT/US00/03565 filed 11 February 2000. Wood et al. was published less than one year prior to the effective filing date of the present invention. Accordingly, Wood et al. is not a 35 U.S.C.102(b) prior art reference.

B. Applicants are also claiming priority to PCT Application No. PCT/US98/19330 filed 16 September 1998 (the same reference being cited as prior art). For the reasons set forth above, Wood et al. is removed as a 35 U.S.C. 102(b) prior art reference.

Withdrawal of this rejection is respectfully requested.

2. Claims 39-43 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Valenzuela et al., WO00/11015 (published 2 March 2000). Valenzuela et al. teaches a polypeptide with allegedly 100% sequence identity to PRO269. Valenzuela et al. teaches antibodies including monoclonal and humanized antibodies. Valenzuela teaches antibody fragments. Valenzuela et al. allegedly teaches antibodies that are diagnostic agents.

A. Applicants have claimed priority to PCT Application No. PCT/US00/03565 filed 11 February 2000. Accordingly, Valenzuela et al. is not prior art since its effective date is after the effective date of the present application.

B. Applicants have claimed priority to Wood et al. (WO99/14328) filed 16 September 1998 under the doctrine of In re Stempel. The Patent Office has stated that Wood et al. (WO99/14328) (to which Applicants claim priority) teaches antibodies to the PRO269 polypeptide. Wood et al. teaches antibodies including monoclonal and humanized antibodies. Wood et al. teaches antibody fragments. Wood et al. allegedly teaches antibodies that are diagnostic agents. Therefore Wood et al. teaches what is taught by Valenzuela. Accordingly, Valenzuela et al. is not prior art since its effective date is after the effective date of the present application of 16 September 1998

Withdrawal of this rejection is respectfully requested.

Rejections under 35 U.S.C. §103

Claim 43 stands rejected under under 35 U.S.C. § 103(a) as being unpatentable over Valenzuela et al. in view of Ramakrishnan et la. (U.S. Patent 5,817,310).

As discussed above, Valenzuela et al. is not prior art because the claims are entitled to the benefit of the 11 February 2000 filing date. Ramakrishnan et al. does not teach the claimed sequence.

Accordingly, the present claims are not obvious over the combination of Valenzuela et al. and Ramkrishnan et al. and Applicants request that this rejection be withdarwn.

CONCLUSION

It is submitted that the present application is in form for allowance, and such action is respectfully requested.

The Commissioner is authorized to charge any additional fees which may be required, including petition fees and extension of time fees, to Deposit Account No. 08-1641 (Docket No. 39780-1618 P2C34).

Respectfully submitted,

Date: May 21, 2004

By: Leslie Mooi
Leslie A. Mooi (Reg. No. 37,047)

HELLER EHRMAN WHITE & McAULIFFE LLP
Customer Number: 35489
275 Middlefield Road
Menlo Park, California 94025
Telephone: (650) 324-7000
Facsimile: (650) 324-0638

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